

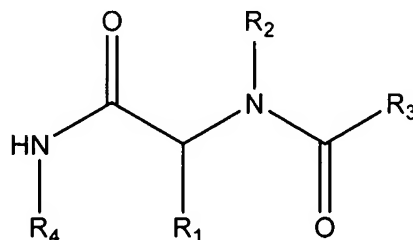
Amendments to the Claims

Please amend Claims 1, 11, 17 and 20. The Claim Listing below will replace all prior versions of the claims in the application:

Claim Listing

What is Claimed is:

1. (Currently amended) A method of inhibiting rejection of a transplanted organ, tissue or cell in a recipient mammal, the method comprising the step of administering to the recipient mammal an effective amount of anti-CD40L monoclonal antibody or rapamycin and an effective amount of a compound represented by the following structural formula:



or a physiological salt thereof, wherein:

R₁ is a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group or a substituted or unsubstituted alkyl group;

R₂ is an optionally substituted aralkyl group or an alkyl group substituted with -NR₅R₆;

R₃ is a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group;

R₄ a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group; and

R_5 and R_6 are independently selected from a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group or R_5 and R_6 taken together with the nitrogen to which they are attached are a non-aromatic heterocyclic group;

wherein each substituted aryl group, substituted alkyl group or substituted aralkyl group are independently optionally substituted at a carbon atom with -OH, -Br, -Cl, -I, -F, R, -CH₂R, -OCH₂R, -CH₂OC(O)R, -OR, -O-COR, -COR, -CN, -NO₂, -COOH, -SO₃H, -NH₂, -NHR, -N(R)₂, -COOR, -CHO, -CONH₂, -CONHR, -CON(R)₂, -NHCOR, -NRCOR, -NHCONH₂, -NHCONRH, -NHCON(R)₂, -NRCONH₂, -NRCONRH, -NRCON(R)₂, -C(=NH)-NH₂, -C(=NH)-NHR, -C(=NH)-N(R)₂, -C(=NR)-NH₂, -C(=NR)-NHR, -C(=NR)-N(R)₂, -NH-C(=NH)-NH₂, -NH-C(=NH)-NHR, -NH-C(=NH)-N(R)₂, -NH-C(=NR)-NH₂, -NH-C(=NR)-NHR, -NH-C(=NR)-N(R)₂, -NRH-C(=NH)-NH₂, -NR-C(=NH)-NHR, -NR-C(=NH)-N(R)₂, -NR-C(=NR)-NH₂, -NR-C(=NR)-NHR, -NR-C(=NR)-N(R)₂, -SO₂NH₂, -SO₂NHR, -SO₂NR₂, -SH, -SO_kR [[and]] or -NH-C(=NH)-NH₂;

wherein each substituted aryl group or substituted aralkyl group are independently optionally substituted at a nitrogen atom, if present, with -R', -N(R')₂, -C(O)R', -CO₂ R', -C(O)C(O)R', -C(O)CH₂ C(O)R', -SO₂R', -SO₂ N(R')₂, -C(=S)N(R')₂, -C(=NH)-N(R')₂, or [[and]] -NR' SO₂R';

R' is hydrogen, an alkyl group, phenyl, -O(Ph), CH₂(Ph), heteroaryl or non-aromatic heterocyclic ring;

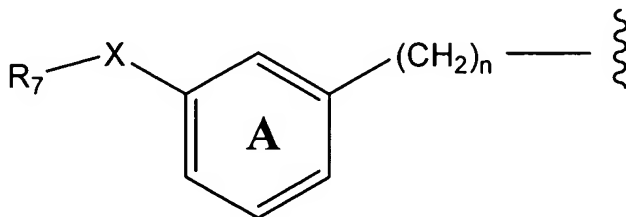
each R is independently an alkyl, benzyl, or aryl group; or -N(R)₂, taken together, can also form a non-aromatic heterocyclic group; and

k is 0, 1 or 2.

2. (Original) The method of Claim 1 wherein the transplanted organ, tissue or cell is a transplanted heart, kidney, lung, liver, pancreas, skin or bone marrow.
3. (Original) The method of Claim 1 wherein the mammal is the recipient of a transplanted stem cell(s).

4. (Original) The method of Claim 1 wherein the transplanted organ, tissue or cell is xenogenic or bio-engineered.
5. (Cancelled)
6. (Cancelled)
7. (Original) The method of Claim 1 wherein R_2 is an optionally substituted heteroaralkyl group or an alkyl group substituted with $-NR_5R_6$.
8. (Original) The method of Claim 7 wherein:
 - a) R_1 is an optionally substituted aryl group or an optionally substituted C_1 - C_4 aralkyl group;
 - b) R_3 is an optionally substituted aryl group or an optionally substituted C_1 - C_4 aralkyl group; and
 - c) R_4 is an optionally substituted aryl group, an optionally substituted cycloalkyl group, an optionally substituted C_1 - C_4 aralkyl group or an optionally substituted C_1 - C_4 cycloalkylalkyl group.
9. (Original) The method of Claim 7 wherein:
 - a) R_1 is an optionally substituted phenyl group or an optionally substituted phenyl- C_1 - C_4 alkyl group;
 - b) R_3 a substituted or unsubstituted phenyl, phenyl- C_1 - C_4 -alkyl, diphenyl- C_1 - C_4 -alkyl, pyrazolyl, pyrazolyl- C_1 - C_4 -alkyl, indolyl, indolyl- C_1 - C_4 -alkyl, thienylphenyl, thienylphenyl- C_1 - C_4 -alkyl, furanylphenyl, furanylphenyl- C_1 - C_4 -alkyl, fluorenyl, fluorenyl- C_1 - C_4 -alkyl, naphthyl, naphthyl- C_1 - C_4 -alkyl, quinoxaliny, quinoxaliny- C_1 - C_4 -alkyl, an optionally substituted quinazolinyl, an optionally substituted quinazolinyl- C_1 - C_4 -alkyl, pyrrolyl, pyrrolyl- C_1 - C_4 -alkyl, thienyl, thienyl- C_1 - C_4 -alkyl, furanyl or furanyl- C_1 - C_4 -alkyl; and

- c) R_4 is an optionally substituted phenyl group, an optionally substituted phenyl- C_1 - C_4 -alkyl group, an optionally substituted diphenyl- C_1 - C_4 -alkyl group, an optionally substituted C_3 - C_8 -cycloalkyl- C_1 - C_4 -alkyl group or an optionally substituted di- $(C_3$ - C_8 -cycloalkyl)- C_1 - C_4 -alkyl group.
10. (Original) The method of Claim 9 wherein R_2 is an optionally substituted imadazolyl- C_1 - C_4 -alkyl group or a C_1 - C_4 alkyl group substituted with $-NR_5R_6$.
11. (Currently amended) The method of Claim 10 wherein:
- R_1 is a phenyl group or phenyl- C_1 - C_4 alkyl group each optionally substituted with R , $-CH_2R$, $-OCH_2R$, $-CH_2OC(O)R$, $-OH$, halogen, $-OR$, $-O-COR$, $-COR$, $-CN$, $-NO_2$, $-COOH$, $-SO_3H$, $-NH_2$, $-NHR$, $-N(R)_2$, $-COOR$, $-CHO$, $-CONH_2$, $-CONHR$, $-CON(R)_2$, $-NHCOR$, $-NRCOR$, $-NHCONH_2$, $-NHCONRH$, $-NHCON(R)_2$, $-NRCONH_2$, $-NRCONRH$, $-NRCON(R)_2$, $-C(=NH)-NH_2$, $-C(=NH)-NHR$, $-C(=NH)-N(R)_2$, $-C(=NR)-NH_2$, $-C(=NR)-NHR$, $-C(=NR)-N(R)_2$, $-NH-C(=NH)-NH_2$, $-NH-C(=NH)-NHR$, $-NH-C(=NH)-N(R)_2$, $-NH-C(=NR)-NH_2$, $-NH-C(=NR)-NHR$, $-NH-C(=NR)-N(R)_2$, $-NRH-C(=NH)-NH_2$, $-NR-C(=NH)-NHR$, $-NR-C(=NH)-N(R)_2$, $-NR-C(=NR)-NH_2$, $-NR-C(=NR)-NHR$, $-NR-C(=NR)-N(R)_2$, $-SO_2NH_2$, $-SO_2NHR$, $-SO_2N(R)_2$, $-SH$ or $-SO_kR$;
- R_3 is represented by the following structural formula:



R_4 is 2,2-diphenylethyl, 2-phenylethyl, benzyl, diphenylmethyl, 1,2-diphenylethyl, 3,3-diphenylpropyl, benzyl, or 2-pyridylethyl, each optionally substituted with $-OH$, halogen, R , $-CH_2R$, $-OCH_2R$, $-CH_2OC(O)R$, $-OR$, $-O-COR$, $-COR$, $-CN$, $-NO_2$, $-COOH$, $-SO_3H$, $-NH_2$, $-NHR$, $-N(R)_2$, $-COOR$, $-CHO$, $-CONH_2$, $-CONHR$, $-CON(R)_2$,

-NHCOR, -NRCOR, -NHCONH₂, -NHCONRH, -NHCON(R)₂, -NRCONH₂,
 -NRCONRH, -NRCON(R)₂, -C(=NH)-NH₂, -C(=NH)-NHR, -C(=NH)-N(R)₂, -C(=NR)-
 NH₂, -C(=NR)-NHR, -C(=NR)-N(R)₂, -NH-C(=NH)-NH₂, -NH-C(=NH)-NHR,
 -NH-C(=NH)-N(R)₂, -NH-C(=NR)-NH₂, -NH-C(=NR)-NHR, -NH-C(=NR)-N(R)₂,
 -NRH-C(=NH)-NH₂, -NR-C(=NH)-NHR, -NR-C(=NH)-N(R)₂, -NR-C(=NR)-NH₂,
 -NR-C(=NR)-NHR, -NR-C(=NR)-N(R)₂, -SO₂NH₂, -SO₂NHR, -SO₂N(R)₂, -SH or -SO_kR;

Ring A is substituted or unsubstituted; R₇ is an optionally substituted phenyl, furanyl, thienyl or pyridyl group; n is an integer from 1-4; and X is a bond, CH₂, OCH₂, CH₂OC(O), CO, OC(O), C(O)O, O, S, SO or SO₂;

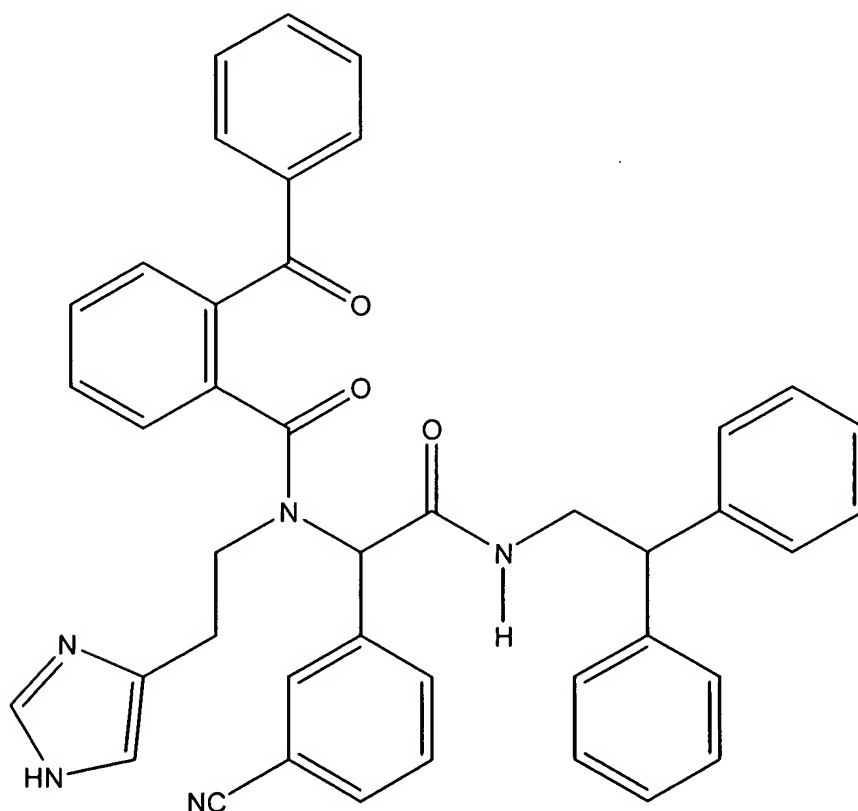
each R is independently C₁-C₄ alkyl or phenyl optionally substituted with amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl; and

k is zero, one or two.

12. (Original) The method of Claim 11 wherein R₁ is a phenyl group or phenyl-C₁-C₂ alkyl group, each optionally substituted with C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, CN, C₁-C₄-alkylthiol, C₁-C₄-haloalkyl or phenoxy; R₄ is 2,2-diphenylethyl, 2-phenylethyl, benzyl, diphenylmethyl, 1,2-diphenylethyl, 3,3-diphenylpropyl, benzyl, or 2-pyridylethyl, each optionally substituted with C₁-C₄ alkyl, C₁-C₄ alkoxy, halogen, CN, C₁-C₄-alkylthiol, C₁-C₄-haloalkyl or phenoxy; R₇ is an optionally substituted phenyl group; n is 1; and X is CO.
13. (Original) The method of Claim 12 wherein Ring A is unsubstituted and R₇ is a phenyl group optionally substituted with R, -CH₂R, -OCH₂R, -CH₂OC(O)R, -OH, halogen, -OR, -O-COR, -COR, -CN, -NO₂, -COOH, -SO₃H, -NH₂, -NHR, -N(R)₂, -COOR, -CHO, -CONH₂, -CONHR, -CON(R)₂, -NHCOR, -NRCOR, -NHCONH₂, -NHCONRH, -NHCON(R)₂, -NRCONH₂, -NRCONRH, -NRCON(R)₂, -C(=NH)-NH₂, -C(=NH)-NHR, -C(=NH)-N(R)₂, -C(=NR)-NH₂, -C(=NR)-NHR, -C(=NR)-N(R)₂, -NH-C(=NH)-NH₂, -NH-C(=NH)-NHR, -NH-C(=NH)-N(R)₂, -NH-C(=NR)-NH₂, -NH-C(=NR)-NHR,

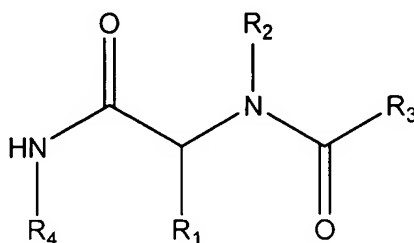
-NH-C(=NR)-N(R)₂, -NRH-C(=NH)-NH₂, -NR-C(=NH)-NHR, -NR-C(=NH)-N(R)₂,
 -NR-C(=NR)-NH₂, -NR-C(=NR)-NHR, -NR-C(=NR)-N(R)₂, -SO₂NH₂, -SO₂NHR,
 -SO₂N(R)₂, -SH or -SO_kR.

14. (Original) The method of Claim 13 wherein R₇ is a phenyl group; and R₂ is 2-(imidazol-4-yl)ethyl.
15. (Previously presented) A method of inhibiting rejection of a transplanted organ, tissue or cell in a recipient mammal, the method comprising the step of administering to the recipient mammal an effective amount of anti CD40L monoclonal antibody and an effective amount of a compound represented by the following structural formula:



or a pharmaceutically acceptable salt of the compound.

16. (Original) The method of Claim 15 wherein the transplanted organ, tissue or cell is a transplanted heart, kidney, lung, liver, pancreas, skin or bone marrow.
17. (Currently amended) A composition comprising anti-CD40L monoclonal antibody or rapamycin and a compound represented by the following structural formula:



or a physiological salt thereof, wherein:

R_1 is a substituted or unsubstituted aryl group or a substituted or unsubstituted alkyl group;

R_2 is an optionally substituted aralkyl group or an alkyl group substituted with $-\text{NR}_5\text{R}_6$;

R_3 is a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group;

R_4 a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group; and

R_5 and R_6 are independently selected from a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group or R_5 and R_6 taken together with the nitrogen to which they are attached are a non-aromatic heterocyclic group;

wherein each substituted aryl group or substituted alkyl group are independently optionally substituted at a carbon atom with $-\text{OH}$, $-\text{Br}$, $-\text{Cl}$, $-\text{I}$, $-\text{F}$, R , $-\text{CH}_2\text{R}$, $-\text{OCH}_2\text{R}$, $-\text{CH}_2\text{OC}(\text{O})\text{R}$, $-\text{OR}$, $-\text{O}-\text{COR}$, $-\text{COR}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{COOH}$, $-\text{SO}_3\text{H}$, $-\text{NH}_2$, $-\text{NHR}$, $-\text{N}(\text{R})_2$, $-\text{COOR}$, $-\text{CHO}$, $-\text{CONH}_2$, $-\text{CONHR}$, $-\text{CON}(\text{R})_2$, $-\text{NHCOR}$, $-\text{NRCOR}$, $-\text{NHCONH}_2$,

-NHCONRH, -NHCON(R)₂, -NRCONH₂, -NRCONRH, -NRCON(R)₂, -C(=NH)-NH₂,
 -C(=NH)-NHR, -C(=NH)-N(R)₂, -C(=NR)-NH₂, -C(=NR)-NHR, -C(=NR)-N(R)₂,
 -NH-C(=NH)-NH₂, -NH-C(=NH)-NHR, -NH-C(=NH)-N(R)₂, -NH-C(=NR)-NH₂,
 -NH-C(=NR)-NHR, -NH-C(=NR)-N(R)₂, -NRH-C(=NH)-NH₂, -NR-C(=NH)-NHR, -NR-
 C(=NH)-N(R)₂, -NR-C(=NR)-NH₂, -NR-C(=NR)-NHR, -NR-C(=NR)-N(R)₂, -SO₂NH₂,
 -SO₂NHR, -SO₂NR₂, -SH, -SO_kR [[and]] or -NH-C(=NH)-NH₂;

wherein each substituted aryl group is optionally independently substituted at a nitrogen atom, if present, with -R', -N(R')₂, -C(O)R', -CO₂ R', -C(O)C(O)R', -C(O)CH₂ C(O)R', -SO₂R', -SO₂ N(R')₂, -C(=S)N(R')₂, -C(=NH)-N(R')₂, [[and]] or -NR' SO₂R';

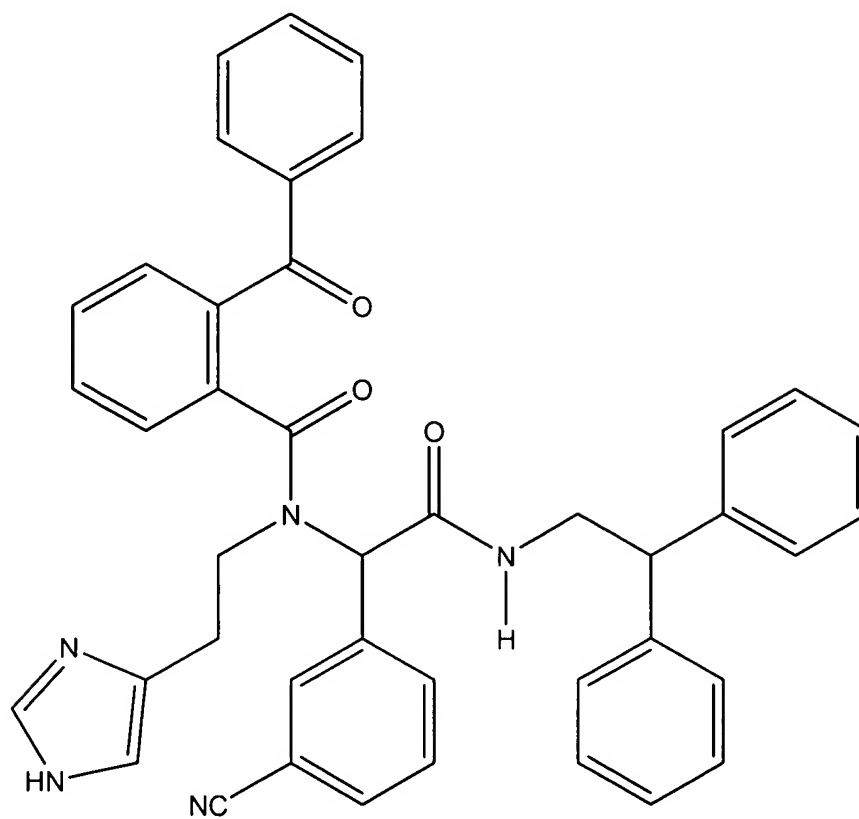
R' is hydrogen, an alkyl group, phenyl, -O(Ph), CH₂(Ph), heteroaryl or non-aromatic heterocyclic ring;

each R is independently an alkyl, benzyl, or aryl group; or -N(R)₂, taken together, can also form a non-aromatic heterocyclic group; and

k is 0, 1 or 2.

18. (Cancelled)

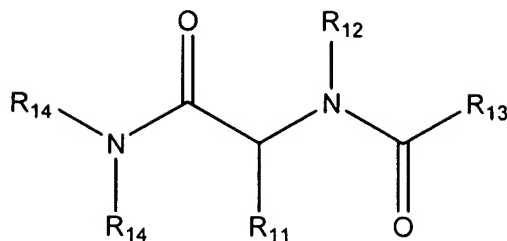
19. (Previously presented) A composition comprising anti CD40L monoclonal antibody and a compound represented by the following structural formula:



or a pharmaceutically acceptable salt of the compound.

20. (Currently amended) A method of inhibiting rejection of a transplanted organ, tissue or cell in a recipient mammal, the method comprising the step of administering to the recipient mammal an effective amount of anti-CD40L monoclonal antibody or rapamycin and an effective amount of a compound represented by the following structural formula:

-11-



R_{11} is -H, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted heteroaryl or a substituted or unsubstituted heteroaralkyl;

R_{12} is alkyl substituted with $\text{NR}_{15}\text{R}_{16}$, a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaralkyl, or a substituted or unsubstituted heterocycloalkylalkyl;

R_{13} is a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, a substituted or unsubstituted aralkyl, a substituted or unsubstituted cycloalkylalkyl, a substituted or unsubstituted heteroaryl, a substituted or unsubstituted heteroaralkyl, a substituted or unsubstituted benzophenonyl, or a substituted or unsubstituted cycloalkylalkyl; and

each R_{14} is independently, -H, a substituted or unsubstituted alkyl, a substituted or unsubstituted aryl, substituted or unsubstituted aralkyl or a substituted or unsubstituted heteroaralkyl;

R_{15} and R_{16} are independently selected from H, a substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted aryl or unsubstituted aralkyl or R_{15} and R_{16} together with the nitrogen to which they are attached are a heterocycloalkyl;

wherein each substituted aryl group, substituted alkyl group, substituted heteroaralkyl, substituted heterocycloalkylalkyl, substituted cycloalkylalkyl, substituted benzophenonyl, substituted cycloalkyl, heterocycloalkyl or substituted aralkyl group are independently optionally substituted at a carbon atom with -OH, -Br, -Cl, -I, -F, R, $-\text{CH}_2\text{R}$, $-\text{OCH}_2\text{R}$, $-\text{CH}_2\text{OC}(\text{O})\text{R}$, -OR, -O-COR, -COR, -CN, $-\text{NO}_2$, -COOH, $-\text{SO}_3\text{H}$, $-\text{NH}_2$, -NHR, $-\text{N}(\text{R})_2$, -COOR, -CHO, $-\text{CONH}_2$, -CONHR, $-\text{CON}(\text{R})_2$, -NHCOR, -NRCOR, $-\text{NHCONH}_2$, $-\text{NHCONRH}$, $-\text{NHCON}(\text{R})_2$, $-\text{NRCONH}_2$, $-\text{NRCONRH}$, $-\text{NRCON}(\text{R})_2$,

-C(=NH)-NH₂, -C(=NH)-NHR, -C(=NH)-N(R)₂, -C(=NR)-NH₂, -C(=NR)-NHR, -C(=NR)-N(R)₂, -NH-C(=NH)-NH₂, -NH-C(=NH)-NHR, -NH-C(=NH)-N(R)₂, -NH-C(=NR)-NH₂, -NH-C(=NR)-NHR, -NH-C(=NR)-N(R)₂, -NRH-C(=NH)-NH₂, -NR-C(=NH)-NHR, -NR-C(=NH)-N(R)₂, -NR-C(=NR)-NH₂, -NR-C(=NR)-NHR, -NR-C(=NR)-N(R)₂, -SO₂NH₂, -SO₂NHR, -SO₂NR₂, -SH, -SO_kR [[and]] or -NH-C(=NH)-NH₂;

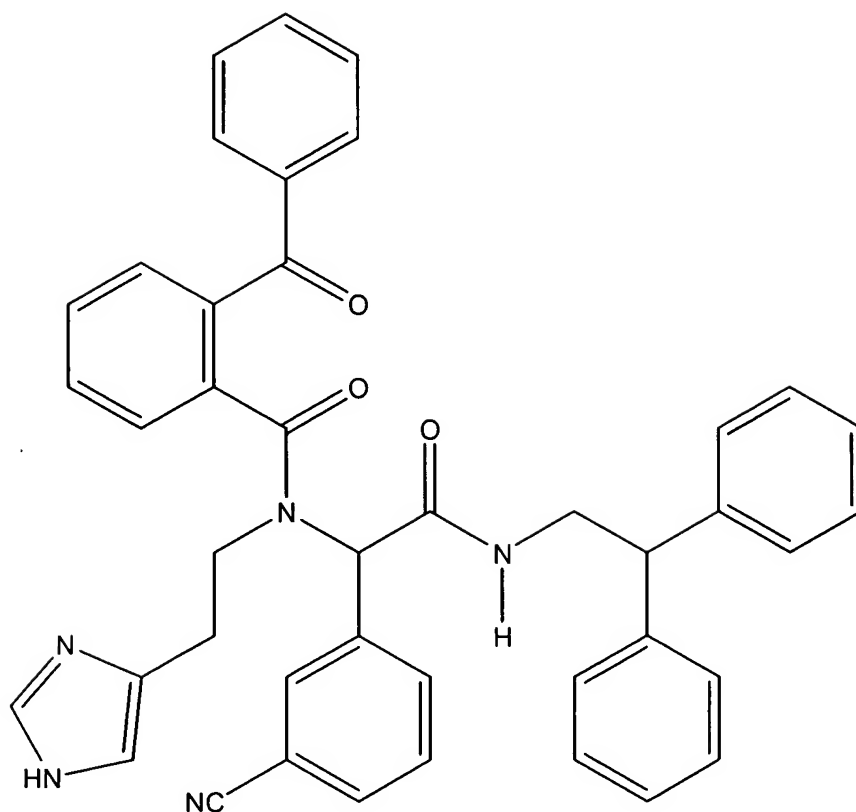
wherein each substituted aryl group, substituted heteroaralkyl, substituted heterocycloalkylalkyl, substituted cycloalkylalkyl, [[,]] heterocycloalkyl or substituted aralkyl group are independently optionally substituted at a nitrogen atom, if present, with -R', -N(R')₂, -C(O)R', -CO₂ R', -C(O)C(O)R', -C(O)CH₂ C(O)R', -SO₂R', -SO₂ N(R')₂, -C(=S)N(R')₂, -C(=NH)-N(R')₂, [[and]] or -NR' SO₂R';

R' is hydrogen, an alkyl group, phenyl, -O(Ph), CH₂(Ph), heteroaryl or non-aromatic heterocyclic ring;

each R is independently an alkyl, benzyl, or aryl group; or -N(R)₂, taken together, can also form a non-aromatic heterocyclic group; and

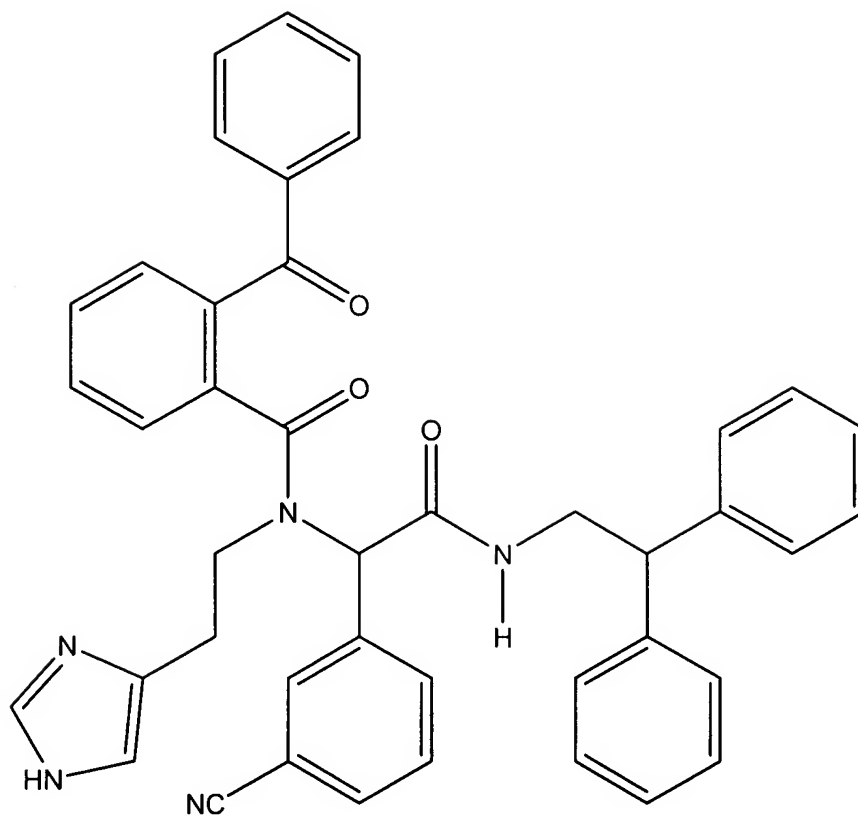
k is 0, 1 or 2.

21. (Previously presented) A method of inhibiting rejection of a transplanted organ, tissue or cell in a recipient mammal, the method comprising the step of administering to the recipient mammal an effective amount of rapamycin and an effective amount of a compound represented by the following structural formula:



or a pharmaceutically acceptable salt of the compound.

22. (Previously presented) The method of Claim 21 wherein the transplanted organ, tissue or cell is a transplanted heart, kidney, lung, liver, pancreas, skin or bone marrow.
23. (Previously presented) A composition comprising rapamycin and a compound represented by the following structural formula:



or a pharmaceutically acceptable salt of the compound.